

BREAST CANCER RISK FACTORS IN AFRICAN-AMERICAN WOMEN: THE HOWARD UNIVERSITY TUMOR REGISTRY EXPERIENCE

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This retrospective case-control study examines risk factors for breast cancer in African-American women, who recently have shown an increase in the incidence of this malignancy, especially in younger women. Our study involves 503 cases from the Howard University Hospital and 539 controls from the same hospital, seen from 1978 to 1987. Using information culled from medical charts, an analysis of various factors for their effect on breast cancer risk was made. The source of data necessarily meant that some known risk factors were missing. Increases in risk were found for known risk factors such as decreased age at menarche and a family history of breast cancer. No change in risk was observed with single marital status, nulliparity, premenopausal status, or lactation. An increased odds ratio was found for induced abortions, which was significant in women diagnosed after 50 years of age. Spontaneous abortions had a small but significant protective effect in the same subgroup of women. Birth control pill usage conferred a significantly increased risk. It is of note that abortions and oral contraceptive usage, not yet studied in African Ameri-

cans, have been suggested as possibly contributing to the recent increase in breast cancer in young African-American women. (*J Natl Med Assoc.* 1993;85:931-939.)

Key words • breast cancer • African-American women

Breast cancer is the most frequent cancer among black and white women of all ages in the United States and comprises 29% of all new cancers in black women.¹ In 1991 alone, an estimated 175 000 cases of invasive breast cancer were diagnosed.¹ There has been a general trend of increasing incidence in women of all races since the 1970s, an increase that is larger in magnitude in blacks than in whites. Although the age-adjusted incidence rate of breast cancer historically has been lower among black women than among white women, a black/white crossover in age-specific risk has been observed since 1969. Among women under the age of 40, the rate has remained higher among black compared with white women, while among women over the age of 40, the rate has remained higher among white women.^{1,2}

Breast cancer is the leading cause of cancer mortality in black women, accounting for 18.8% of total cancer deaths. In white women, despite accounting for 19.7% of cancer deaths, breast cancer comes second to lung cancer (21.1%). Specifically among women under the age of 50, the mortality rate in whites has declined, while it has increased in blacks.^{1,2} Other facts that underscore the differences in breast cancer statistics between blacks and whites include the finding of an excess of estrogen receptor negative tumors^{3,4} in blacks and race as an independent predictor of survival.⁵⁻⁷

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TABLE 1. SUMMARY OF RESULTS FOR ALL VARIABLES ANALYZED

Variable	Result
Age at menarche	Significantly increased risk for age of 13 to 14 years at menarche (reference group: age at menarche ≥ 15 years)
Parity	No change in risk with nulliparity or three to four births while one to two births seem to protect (reference group: at least five children)
Abortions	Significantly increased risk in women over the age of 50
Miscarriages	Significant protective effect in women over the age of 50
Menopausal status	No change in risk
Marital status	Divorced, separated, and widowed women seem to be protected while there is no change in risk for single women (reference group: married women)
Family history	Increased risk for women with a first-degree female relative
Birth control pill usage	Increased risk for ever having used the pill
Lactation	No change in risk

To date, few studies have addressed risk factors for breast cancer primarily in blacks.⁸⁻¹¹ Austin et al⁸ and Schatzkin et al⁹ conducted hospital-based case-control studies and concluded that the risk factor profile in black women appeared similar to that observed in whites. A similar conclusion was made by Amos et al¹⁰ on the risk conferred by a first-degree family history. Austin et al⁸ and Devesa and Diamond¹¹ both found a positive association of breast cancer to education.

To explain the differences in breast cancer rates between black and white women, Gray et al¹² first suggested that this could be due in part to differences in their age at menarche (risk factor more important in premenopausal women and earlier in blacks), age at first birth (risk factor mainly in women over the age of 40 and earlier in blacks), and age at menopause (earlier in blacks). Both Krieger¹³ and White et al,¹⁴ who studied the effects of socioeconomic factors on breast cancer, suggested that the cause of the increased incidence among all young women might include earlier age at menarche, later age at first live birth, and a decreasing number of births per woman. Factors hypothesized to play a larger role in blacks included changes in diet, and two newer, tentative risk factors: oral contraceptive usage and

induced abortions. However, the risk for breast cancer conferred by these two factors, studied mainly in whites, remains controversial.¹⁵⁻²²

The availability of a hospital tumor registry serving a largely black population in one of the areas with the highest breast cancer mortality in the United States¹ allowed us to perform a retrospective study of postulated risk factors associated with this disease. This study included data on oral contraceptive usage and abortions, neither of which has been studied in blacks before.

SUBJECTS AND METHODS

The Howard University Tumor Registry has maintained a database of all cancer cases diagnosed in the hospital since 1960. The cases for this study were African-American women with histologically confirmed breast cancer seen at Howard University Hospital between 1978 and 1987 inclusive. This period was selected because the data have been recorded more systematically in the Registry since 1978. The hospital is one of several in the Washington, DC metropolitan area.

Controls were African-American patients from the hospital, who were admitted with nonmalignant conditions and matched for 5-year age group. Women with psychiatric conditions and those with a history of drug abuse were excluded from the study because the reliability of the data obtained from such patients is low.

Data for the cases were abstracted from the Tumor Registry records and supplemented with information from the medical charts. Information for the controls came from patient charts.

The study population was comprised of 503 cases and 539 controls. A detailed description of the clinical and histological characteristics of the cases were reported previously.²³ The mean \pm standard deviation age at diagnosis was 57.2 ± 14.6 years for the cases and 56.1 ± 14.4 years for the controls. More than 95% of both the cases and the controls lived in the District of Columbia or in the state of Maryland. The variables that could be retrieved for both cases and controls included age at menarche, parity, number of abortions and miscarriages, menopausal status, marital status, family history of breast cancer, oral contraceptive usage, and lactation.

Analysis

For a given risk factor, the odds ratio (OR) was estimated using the category with the baseline risk judged from the literature as the reference group. Odds ratio estimates first were made using simple stratifica-

TABLE 2. DISTRIBUTION OF CASES AND CONTROLS ACCORDING TO AGE AT MENARCHE

Age at Menarche	Cases	Controls	COR* (CI ₉₅)	LOR* (CI ₉₅)
All Women				
≥15 years†	61	93	1.0	1.0
13 to 14	220	176	1.9 (1.3-2.8)	1.9 (1.3-3.0)
11 to 12	161	193	1.3 (0.9-1.9)	1.2 (0.8-1.8)
≤10	34	55	0.9 (0.6-1.6)	0.9 (0.5-1.7)
Premenopausal				
≥15 years†	7	18	1.0	1.0
13 to 14	35	38	2.4 (0.9-6.3)	2.5 (0.9-7.4)
11 to 12	40	64	1.6 (0.6-4.2)	1.4 (0.5-4.0)
≤10	7	18	1.0 (0.3-3.4)	0.7 (0.2-2.9)
Postmenopausal				
≥15 years†	51	75	1.0	1.0
13 to 14	144	136	1.6 (1.0-2.4)	1.9 (1.2-3.0)
11 to 12	95	127	1.1 (0.7-1.7)	1.7 (0.7-1.9)
≤10	26	36	1.1 (0.6-2.0)	1.0 (0.5-2.0)

*COR and LOR are the crude and multiple logistic estimates of the odds ratio.

†Reference group.

tion on age at diagnosis. The Mantel-Haenszel estimate of the common odds ratio over the age strata (AOR) was calculated whenever the test for homogeneity of the stratum-specific ORs was not significant.²⁴ When the numbers were too small to allow adjustment for age or when the stratum-specific ORs were not homogeneous, the crude odds ratios (CORs) were reported.

Next, multiple logistic regression was performed to allow for simultaneous adjustment for several risk factors. Logistic regression was conducted on a subset of 405 cases and 463 controls, for which complete data were available. The logistic regression equation included age at diagnosis as a continuous variable, and categorical terms for age at menarche, parity, induced abortion, miscarriage, menopausal status, marital status, and family history. Results from this analysis are denoted LOR.

Use of the birth control pill was examined in the subset of women born after 1940 and breast-feeding was examined among parous women only. All analyses were performed using the software package SAS.²⁵

RESULTS

Table 1 summarizes the results.

Age at Menarche

The data did not show the expected trend of an increasing risk for breast cancer with decreasing age at menarche. Only those women who experienced men-

arche at 13 to 14 years showed a significantly increased risk relative to the reference group (age at menarche >15 years) (Table 2). The LOR estimate was 1.9 (95% confidence interval [CI₉₅]=1.3-3.0). When age at menarche was examined separately by menopausal status, this increased OR remained significant only in the postmenopausal group. When all the women with age at menarche <15 were treated as a group, the OR adjusted on age was borderline significant: OR = 1.5 (CI₉₅ = 1.1-2.2).

Parity

Parity was defined as the number of pregnancies carried to term irrespective of outcome. However, it corresponded closely to the number of live births since there were so few stillbirths reported: 2 among cases and 15 among controls. Compared with having at least five births, nulliparity and three to four births conferred no increased risk, while the group with one to two births appeared to be protected from breast cancer (LOR = 0.5; CI₉₅ = 0.4-0.8) (Table 3).

Marital Status

When marital status was studied, the divorced, separated, and widowed women were tested as one group (D/S/W), single women as another, and married women as a third. Relative to married women, each of the alternative groups seemed to be protected from breast cancer, with the OR values

TABLE 3. ODDS RATIOS FOR VARIOUS FACTORS ANALYZED

Variable	Cases	Controls	AOR* (CI ₉₅)	LOR† (CI ₉₅)
Menopausal Status				
Postmenopausal‡	334	386	1.0	1.0
Premenopausal	94	148	0.6 (0.4-1.0)	1.0 (0.6-1.6)
Parity				
≥5‡	122	99	1.0	1.0
3 to 4	106	121	0.7 (0.5-1.0)	0.6 (0.4-1.0)
1 to 2	153	203	0.6 (0.4-0.9)	0.5 (0.4-0.8)
0	122	116	0.9 (0.6-1.2)	0.8 (0.5-1.3)
Marital Status				
Married‡	204	176	1.0	1.0
D/S/W	176	224	0.7 (0.5-0.9)	0.5 (0.4-0.8)
Single	87	125	0.6 (0.4-0.9)	0.7 (0.4-1.0)
Birth Control Pill Usage§				
Never‡	31	85	1.0	1.0
Ever	27	10	7.7 (3.5-17.2)	5.5 (1.1-27.1)
Lactation History 				
Never‡	124	335	1.0	1.0
Ever	28	43	1.8 (1.1-3.0)	1.3 (0.7-2.5)

*Odds ratios are all age-adjusted except that for lactation, which is a crude value.

†Multiple logistic estimate of the odds ratio.

‡Reference group.

§Restricted to women born after 1940.

|| This variable was analyzed among parous women only.

adjusted on age only being less than 1.0 (Table 3). However, after adjusting for all other variables in the logistic regression, the protective effect remained significant only in the D/S/W group: LOR = 0.5 (CI₉₅ = 0.4-0.8).

Menopausal Status

Most of the women included in this study were postmenopausal: 78% of cases and 72% of controls. With respect to menopausal status, the OR for premenopausal relative to postmenopausal women was not significantly different from 1 in either the logistic regression or stratified analyses. The LOR was 1 (CI₉₅ = 0.6-1.6) (Table 3).

Birth Control Pill Usage

The women included in this analysis were all born after 1940, thus they were over the age of 20 years by 1960 when the pill was introduced. Birth control pill usage conferred an increase in the OR (LOR = 5.5; CI₉₅ = 1.1-27.1) (Table 3).

Breast-Feeding

Breast-feeding was examined only among parous women, among whom information was available on 152 cases and 378 controls. After adjusting for all other variables, no significant effect of lactation on breast cancer risk was observed. The LOR estimate was 1.3 (CI₉₅ = 0.7-2.5) (Table 3).

Family History

The risk associated with a positive family history of breast cancer was computed with respect to first degree relatives only, since there was no information in controls of a family history of breast cancer in a second-degree relative. No daughters were reported as having breast cancer either; therefore, all of the first-degree female relatives were mothers or sisters. A family history of breast cancer in one relative (mother or sister) conferred an increased risk of 8.3 (CI₉₅ = 3.4-20.3) (Table 4). Moreover, there was a total of 11 cases with more than one affected relative. The OR could not be estimated for these cases because there were no such

TABLE 4. DISTRIBUTION OF CASES AND CONTROLS ACCORDING TO FIRST-DEGREE FAMILY HISTORY

	Controls	Cases	COR* (CI ₉₅)
Negative family history	477	432	
Positive family history			
Mother only	4	28	7.7 (2.0-29.6)
Sister only	4	32	8.8 (2.3-33.4)
One first-degree relative†	8	60	8.3 (3.4-20.3)
Mother and sister	0	2	—
Two sisters	0	6	—
Two sisters and mother	0	1	—
Mother and father	0	1	—
Mother and brother	1	1	—
Total	9	71	—

*Only the crude odds ratio is presented because there were so few controls with a positive first-degree family history.

†This category includes women whose mother or sister is affected with breast cancer.

TABLE 5. DISTRIBUTION OF CASES AND CONTROLS ACCORDING TO A HISTORY OF INDUCED ABORTIONS AND MISCARRIAGES*

Variable	Cases	Controls	COR† (CI ₉₅)	LOR† (CI)
Induced Abortions				
≤40 years				
Never‡	42	52	1.0	1.0
Ever	15	15	1.2 (0.5-2.8)	1.5 (0.7-3.5)
41 to 49 years				
Never‡	44	63	1.0	1.0
Ever	19	10	2.7 (1.1-6.4)	2.8 (1.0-8.1)
≥50 years				
Never‡	213	233	1.0	1.0
Ever	55	13	4.6 (2.5-8.7)	4.7 (2.6-8.4)
Miscarriages§				
≤40 years				
Never‡	42	52	1.0	1.0
Ever	10	11	1.1 (0.4-2.9)	1.3 (0.5-3.3)
41 to 49 years				
Never‡	44	63	1.0	1.0
Ever	17	19	1.3 (0.6-2.7)	1.0 (0.3-2.7)
≥50 years				
Never‡	213	233	1.0	1.0
Ever	63	105	0.7 (0.5-0.9)	0.6 (0.4-0.9)

*For the crude odds ratios, the reference group comprised women who had neither induced abortions nor miscarriages.

†COR and LOR are the crude and multiple logistic estimates of the odds ratio.

‡Reference group.

§The odds ratio controlling for this age stratification only was 0.8 (CI₉₅ = 0.6-1.1).

reports among the controls.

Induced Abortions

Women with at least one induced abortion consistently had a risk >1 relative to those who had none. Because the homogeneity test for the three age-at-diagnosis strata (<40 years, 41 to 49 years, and ≥50

years) was significant ($P = .04$), the crude and adjusted ORs were calculated in each age stratum. As seen in Table 5, the LOR was not significant in women either <40 years or between 41 and 49 years, but was significantly raised in those ≥50 years at diagnosis: LOR = 4.7 (CI₉₅ = 2.6-8.4). It is of note that while in the three age strata the proportions of abortion reported in

TABLE 6. COMPARISON OF SELECTED VARIABLES IN DIFFERENT FEMALE POPULATIONS

Variable	Howard Univ Hospital		NHANES I	
	Cases (N=503)	Controls (N=539)	Blacks (N=1058)	Whites (N=6065)
Mean age \pm standard deviation	57.2 \pm 14.6	56.1 \pm 14.4	56.1 \pm 14.4	56.2 \pm 14.9
Induced abortion (ever)				
≤ 40	26%	22%	—	—
41 to 49	30%	14%	—	—
≥ 50	20%	5%		
Miscarriage (ever)				
≤ 40	19%	17%	20%	24%
41 to 49	28%	23%	34%	29%
≥ 50	20%	31%	36%	27%
Family history of breast cancer	12.2%	1.6%	2.8%	6.4%
Nulligravidity among single women*	14%	16%	29%	90%
Nulliparity among single women*	25.3%	29.6%	40%	94.2%
Oral contraceptive usage (ever)	47%	10%	71%	75%

*Numbers of single women in the various groups were as follows: Howard Univ cases=87, Howard Univ controls=125, NHANES I blacks=81, and NHANES I whites=271.

cases were 26%, 30%, and 20% (Table 6), the corresponding proportions in controls were 22%, 14%, and 5%. The ORs according to the number of induced abortions were not computed within the age strata because of the small sample sizes.

Miscarriages

A significant protective effect of miscarriages on breast cancer was observed in women diagnosed with breast cancer after 50 years of age (LOR=0.6; CI_{95} =0.4-0.9) (Table 5). In the two younger age groups, neither the crude nor the logistic regression estimates of the ORs differed significantly from 1. However, the homogeneity test over the three age strata was nonsignificant, and the overall OR did not differ from 1 (age-adjusted OR=0.8 (CI_{95} =0.6-1.1)). The rate of miscarriages increased with age among controls while varying less among the cases (Table 6). When examined according to the number of miscarriages, the OR for all women remained close to 1.

DISCUSSION

In this study, some risk factors were found associated with breast cancer as previously reported, others led to unexpected results, and new ones, rarely studied in blacks, appeared to increase the risk for breast cancer.

The statistically significant increase in breast cancer risk found in postmenopausal women with ages at menarche between 13 and 14 years (as compared to

after 15 years) is similar to the results reported by Schatzkin et al.⁹ However, the trend of decreasing risk with increasing age at menarche observed by Schatzkin et al⁹ was not seen in our data. Austin et al⁸ also were unable to demonstrate a clear relationship between breast cancer and age at menarche. Although usually reported as a risk factor in whites, age at menarche may have a relatively small effect on breast cancer, since the estimate of the OR associated with it is usually <2 .^{26,27}

Menopausal status was not significantly associated with breast cancer in our sample. Missing data on age at menopause for most women did not allow a more detailed analysis of this variable. A trend of increasing risk with increasing age at menopause was found in two of the previous studies in black women.^{8,9} Although most of the literature supports late age at menopause as a risk factor for breast cancer, its effect is relatively small and sometimes does not reach significance.²⁶⁻²⁸

Our study confirmed the association between positive family history and breast cancer, which has been documented in both blacks and whites. Our OR estimate of 8.3 is higher than the published values, which range from 1.6 to 3.4.^{9,10,28-33} The literature shows considerable variation in the report rate of positive family history among cases (4.9% to 22.2%) and controls (1.5% to 12.1%). The National Health and Nutrition Examination Survey (NHANES I)³⁴ epidemiologic follow-up dataset for 1984 has report rates of 2.8% among blacks and 6.4% among whites (Table 6).

TABLE 7. COMPARISON OF PARITY IN WOMEN OF DIFFERENT MARITAL STATUS FROM HOWARD UNIVERSITY HOSPITAL AND NHANES I DATA (1984)

Marital Status	Howard Univ Hospital		NHANES I	
	Cases	Controls	Blacks	Whites
N	467	525	978	6017
Married	3.1 (3)*	2.7 (2)	3.8 (3)†	2.9 (3)
D/S/W	2.6 (2)	2.7 (2)	3.6 (3)†	2.9 (2)
Single	2.7 (2)	2.0 (2)	2.2 (1)‡	0.1 (0)
P§	.27	<.01	<.001	0.000
M/S	1.1	1.3	1.9	29

*Mean number of children given with median value in parentheses.

†Level of significance for difference between mean parity values for the three black groups ($P < .001$).

‡Level of significance for difference between mean parity values for the three black groups ($P = .11$).

§Level of significance for difference between mean values of parity for single and married women.

|| Ratio of mean parity values for married and single women.

Our rates among cases (12.2%) and controls (1.6%) are respectively close to the average and lowest published values. This suggests the possibility of underreporting in controls, partly accounting for our high risk estimate. However, it should be noted that the importance of genetic factors in breast cancer among blacks has yet to be studied systematically.

Two variables related to reproductive history, parity, and marital status, led to unexpected results. Nulliparity and three to four births did not modify the risk, but parity of one to two births conferred a significantly decreased risk relative to parity of at least five births. Nulliparity was demonstrated by Schatzkin et al⁹ to significantly increase the risk of breast cancer. However, Austin et al⁸ did not find a significant association. Indeed, while some authors have confirmed an independent effect of parity on breast cancer,³⁵ others claimed it could only act through age at first birth.³⁶ Our results might be partly explained by the possibility of a pattern of age at first birth in our data. However, age at first birth was not consistently recorded, so our study could not account for it.

The other surprising result was that single women had no change in risk, and divorced, separated, and widowed women (D/S/W) had a decreased OR compared with married women. The increase in risk reported in white single women compared with white married women may reflect differences in reproductive experience related to socioeconomic status. The role of socioeconomic status could not be determined from our data. With respect to parity, the three marital status groups of cases did not differ significantly in our sample. The mean number of births was 2.7 in single women, 2.6 among the divorced, separated, and widowed women, and 3.1 among the married ones.

Table 7 shows a comparison of the present dataset with the NHANES I data.³⁴ Although there is a significant difference between the mean values of parity in the single and married women from both the Howard University Hospital and NHANES I samples of black controls, this difference is not as striking as that observed in the white controls. Moreover, we noted that the proportion of single women never having been pregnant in the NHANES I dataset³⁴ was only 29% in the black women as opposed to 90% in whites. Our data had even lower proportions, with 16% of controls and 14% of cases being nulligravidae (Table 6). It seems possible that single black women may be more similar in their reproductive experience to married black women than is the case in whites.

Whereas the literature is still highly controversial on the issue of abortions, our results indicated that induced abortions may significantly increase the risk of breast cancer in black women, while a history of miscarriages may act as a protective factor, especially in women >50 years. Our overall abortion report rate of 22.9% in cases and 9.8% in controls compares with the published range of 1% to 19.7% in cases of 1% to 15.6% in controls.^{15,18,37} However, when examined by age at diagnosis, the rates of induced abortion did not vary much among cases (20% to 30%), while they decreased from 22% to 5% with increasing age among the controls (Table 6). This suggests possible underreporting among the older controls, accounting for the high OR observed in the women diagnosed after age 50. Conversely, the protective effect of miscarriages does not appear to be due to a bias, since the report rate in our controls compares well with that from the NHANES I data (Table 6).³⁴ Such a comparison was not possible for abortions because they were not recorded in the

NHANES I data.

The controversial results reported in whites stem partly from the fact that these studies differed in the type of data and methods of analysis.^{15-18,37} Induced and spontaneous abortions (miscarriages) were not always distinguished, and the timing of abortions relative to the first full-term pregnancy was not always taken into account. Variations also occurred between studies in the age group and parity of their subjects. Considering miscarriages and abortions as one group, Pike et al¹⁵ reported a significantly increased risk for breast cancer among young women only when the termination of pregnancy occurred prior to a first full-term pregnancy, whereas Vessey et al¹⁷ in another study did not find a significant result in the same subgroup.

In studies distinguishing between abortions and miscarriages and adjusting for age at first full-term pregnancy, Brinton et al³⁷ and Rosenberg et al¹⁸ did not document any significant association with breast cancer, whether in parous or nulliparous women. However, a significant protective effect of miscarriages was found by Rosenberg et al¹⁸ only in parous women who had at least three miscarriages. On the contrary, a positive association of breast cancer with miscarriages was reported by Hadjimichael et al¹⁶ only in uniparous women. As mentioned earlier, no study known to us had addressed the question of abortions as a risk factor for breast cancer in blacks prior to the present.

Use of the birth control pill was associated with an increased OR of 5.5 (CI₉₅ = 1.1-27.1). Only the overall risk of ever-use of oral contraceptives could be computed since in this retrospective study, age at first usage, time of usage with respect to the first live birth, duration of usage, and type of birth control pill were not recorded. The proportion of ever-users of oral contraceptives in our relevant dataset was 10% in controls and is lower than the published range of 34% to 82% in other studies^{15,17,22,38-42} and the value obtained from the NHANES I data,³⁴ which was 71% in black women born after 1940 (Table 6).

The issue of birth control pill usage as a risk factor for breast cancer is still a matter of dispute. Even though most initial studies did not report any significant association,^{22,43} an increased risk of breast cancer with oral contraceptive use in young women recently was found by several authors.^{38,42,44-46} The importance of timing of use (relative to first full-term pregnancy or before the age of 25 years) and total duration of use have yet to be resolved. Whether the risk persists in older women or when oral contraceptives are used at later ages also is uncertain.

Breast-feeding had no significant effect on the risk for breast cancer in our data. However, it should be noted that a large number of cases had missing information on this variable, and the effect of this selection is unexplored. This is another factor that is still of uncertain effect. While some studies have found a significant protective effect of lactation even after correcting for the age at first birth,^{21,28} others found none.³⁷

CONCLUSION

The results of this study confirm the role of family history and earlier age at menarche as risk factors for breast cancer and suggest a possible effect of new ones: induced abortions and oral contraceptive use. Bearing in mind the missing information on possible confounders, eg, socioeconomic status and age at first birth, these results are tentative. However, they underscore the need for carefully delineating lifestyle factors, particularly those related to reproductive history and birth control practices as well as genetic factors.

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